New Macrocyclic Polyethers with Remote Binding Sites

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The synthesis and binding properties of new macrocyclic polyethers are described. These systems incorporate 2,2'-bipyridyl functions in such a fashion that binding of metal nuclei can occur at either the macrocycle or the bipyridyl function. Evidence is presented that binding of alkali metals occurs at the crown ether cavity while binding of transition metals occurs at the bipyridyl function. Simultaneous binding of two different metals is interpreted in terms of electronic and allosteric effects.

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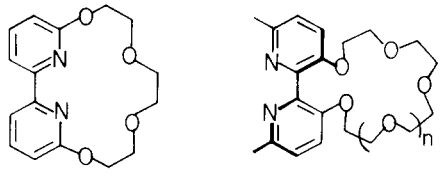
A number of macrocyclic polyethers which incorporate the 2,2' bipyridyl function have been described (1). These substances, *e.g.*, **1** (Figure 1) have invariably been constructed in such a manner that the pyridyl nitrogens can be directed toward, and modify the binding properties of, the ether cavity. As part of our study of the effects of remote binding forces on rates (2) and equilibria (3) we have prepared the new macrocycles **2** in which the pyridyl nitrogens are directed away from the crown ether cavity and provide a secondary binding site. Here we describe their synthesis and binding properties.

Fig. 1



1

2
a, n = 1
b, n = 2

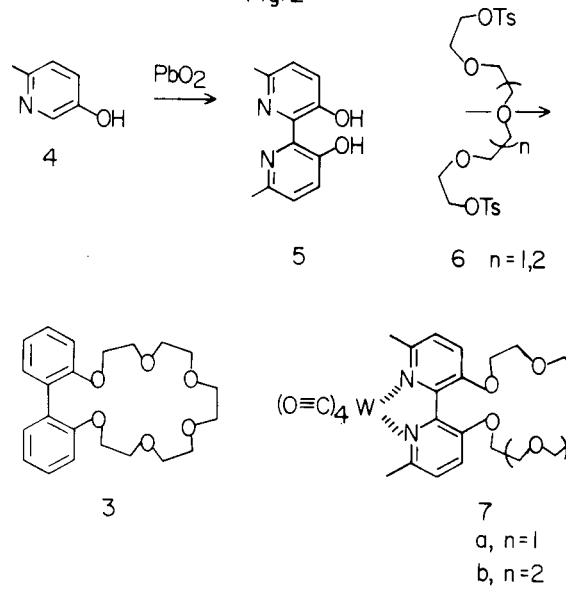
Synthesis.

The bipyridyl function was constructed by oxidative coupling of the pyridynol **4** (Figure 2) following a patented procedure (4). Condensation of **5** with the appropriate ditoysylates **6** afforded 40-50% yields of **2**. The chelates **7** were obtained by heating **2** with $W(CO)_6$ in xylene. The biphenyl analog **3** was also prepared for comparison purposes.

Binding.

Binding to alkali metals was determined using the procedure of Pedersen (5) as modified by Cram (6). Alkali and ammonium picrates were extracted from aqueous solutions into chloroform containing the crown ethers, picrate was determined by the ultraviolet absorbance, and association constants K_a, (Table 1) were calculated using literature values (6) for the distribution constants, K_d, for the various picrates. In addition, the K_d for $Na^+ BPh_4^-$ was determined and this salt was used to assess binding of Na^+ to tungsten complexes **7**.

Fig. 2



4

5

6 n = 1,2

3

7
a, n = 1
b, n = 2

Table 1

Association Constants Determined by Extractions $K_a \times 10^{-3}$

	Picrates			$Na^+ BPh_4^-$			
	2a	**2b**	**3**	**2a**	**2b**	**7a**	**7b**
Li	97	140	27				
Na	105	260	210	7	90	4.5	8
K	33	590	540				
NH_4	41	200	210				
Rb	36	220	230				
Cs	8	65	93				

Discussion.

The similarity of the binding characteristics of **2b** and **3** toward alkali metals leaves little doubt that the ethereal portion of **2**, rather than the bipyridyl function, is the site of binding (7). Moreover, the modest preference of **2a** for the smaller ions Li^+ and Na^+ and the preference of **2b** and **3** for K^+ are consistent with the accepted relationship between cavity dimension and ionic radius in binding selectivity (8). The situation with the tungsten complexes is less clear. Chelation at the bipyridyl function must reduce the

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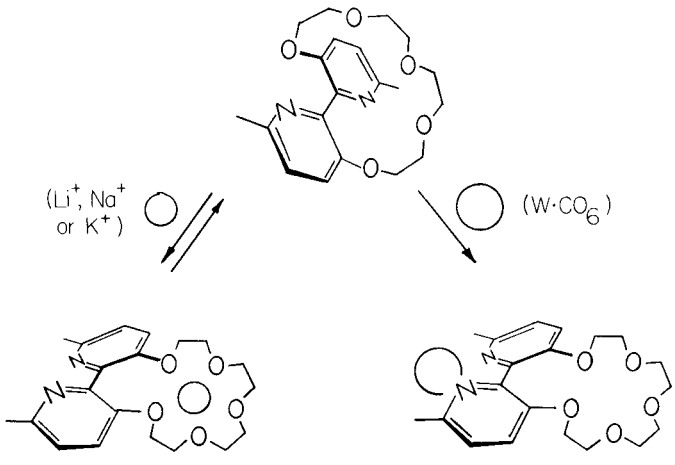
number of conformations available to the crown ether and thereby limit the effective size of that cavity (Figure 3). However, electronic factors, transmitted to the aryl oxygens, will also alter the binding capacity of the crown cavity (9). The diminished affinity of **7** to Na^+ can be attributed to either or both of these factors; the former can be regarded as an allosteric effect while the latter is merely an inductive effect. Our current research efforts involving the changes in ion selectivity in bound complexes **7** are directed at resolving this issue.

Fig. 3



EXPERIMENTAL

2,2'-Bis-(6-methyl-3-pyridinol) (**5**).

This compound was prepared by adding 6-methyl-3-pyridinol (1.09 g., 10 mmoles) to a stirred suspension of lead dioxide (2.38 g., 10 mmoles) in 100 ml. of hot benzene followed by refluxing overnight. The lead residue obtained by filtering the cooled reaction mixture was treated with disodium EDTA (3.72 g., 10 mmoles) in 100 ml. of water in the presence of 100 ml. of chloroform. After 2 hours of stirring the organic layer was separated, filtered, and added to the benzene filtrate. Upon evaporation, the tan solid obtained was chromatographed on ~ 50 g. of silica gel (60-200 mesh) eluting with ethyl acetate. Recrystallization from petroleum ether gave 0.22 g. (40%) of yellow-green fluorescent crystals, m.p. 189-190° (lit. (4) m.p. 189-190°); nmr (deuteriochloroform): 90 MHz δ 2.76 (s, 6), 7.35 (d, J = 9 Hz), 7.58 (d, J = 9 Hz).

Bipyridyl Crown Ethers **2a** and **b**.

The following general procedure, given for **2a**, was employed. 2,2'-Bis-(6-methyl-3-pyridinol) **4** (0.9595 g., 4.4 mmoles) in 400 ml. of dry THF was treated under nitrogen with freshly sublimed potassium *t*-butoxide (1.05 g., 9.4 mmoles) and tetraethylene glycol ditosylate (10) (2.43 g., 4.8 mmoles) and heated under reflux for 2 days. The cooled solution was quenched by the addition of 10 ml. of cold water followed by evaporation of the volatiles. The residue, in 300 ml. of chloroform was extracted into 1*N* hydrochloric acid (3 × 100 ml.) and the combined aqueous phases were neutralized with 2.5*N* sodium hydroxide then extracted with 3 × 100 ml. of chloroform. Evaporation of the combined organic phases gave the crude product which was purified by column chromatography on alumina using acetone-dichloromethane (3:7) as eluent. Kugelrohr evaporation of the volatiles in the appropriate fractions gave 0.83 g. (50%) of **2a** as an oil; nmr (deuteriochloroform): δ 2.58 (s, 6), 3.6 (m, 12), 4.05 (m, 4), 7.12, 7.25 (AB q, J = 9 Hz, 4).

Anal. Calcd. for $C_{20}H_{26}N_2O_5$: 374.1841; C, 64.15; H, 7.00; N, 7.48. Found: C, 374.1843; C, 64.04; H, 7.22; N, 7.33.

With pentaethylene glycol ditosylate the procedure afforded **2b** (40%); nmr (deuteriochloroform): δ 2.55 (s, 6), 3.6 (m, 16), 4.06 (m, 4), 7.13, 7.23 (AB q, J = 8 Hz, 4).

Anal. Calcd. for $C_{22}H_{30}N_2O_6$: 418.2103; C, 63.14; H, 7.23; N, 6.69. Found: 418.2103; C, 63.30; H, 7.41; N, 6.86.

Biphenyl Crown Ether **3**.

This compound was obtained as a low melting solid in 61% yield by the general procedure, using *o,o*-biphenol and pentaethylene glycol ditosylate, but without acid extractions before chromatography, m.p. 51-53°; nmr (deuteriochloroform): δ 3.5 (m, 16), 4.0 (m, 4), 6.9 (m, 4), 7.18 (m, 4).

Anal. Calcd. for $C_{22}H_{28}O_6$: 388.1885; C, 68.38; H, 6.78. Found: 388.1868; C, 68.15; H, 7.04.

Distribution Constant (K_d) for Sodium Tetraphenylborate.

Aqueous .01*M* sodium tetraphenylborate solution (200 ml.) was shaken in a sealed separatory funnel with 300 ml. of ethanol-free chloroform. The layers were allowed to separate and clarify (24 hours) and the lower layer was transformed to a flask where the solvent was evaporated under vacuum. The residue was quantitatively transferred with water to a 5.00 ml. volumetric flask and diluted with water to the mark. The uv spectrum of this solution was used to calculate the amount of salt extracted into the original chloroform layer; λ max 272 nm, ε 1,663. The value for K_d was obtained using the following equation and based on 3 determinations.

$$K_d = \frac{[Na^+ B\varnothing_4^-]_{CHCl_3}}{[Na^+]_{H_2O}[B\varnothing_4^-]_{H_2O}} = .22 \pm .01$$

Tungsten Complexes **7a** and **7b**.

These compounds were prepared in quantitative yield as follows: **2a** (0.0717 g., 0.19 mmol) and $W(CO)_6$ (0.0742 g., 0.21 mmole) were heated at reflux in xylene under nitrogen for 3 hours. Cooling and dilution with petroleum ether gave a dark red precipitate which was triturated with hexane and dried *in vacuo* to give **7a** as dark red crystals, m.p. 100° dec; nmr (deuteriochloroform): 100 MHz δ 2.82 (s, 6), 3.6 (m, 12), 4.05 (m, 4), 7.3 (m, 4).

From **2b** and $W(CO)_6$ the procedure afforded **7b**, m.p. 130° dec; nmr (deuteriochloroform): 60 MHz δ 2.95 (s, 6), 3.7 (m, 16), 4.07 (m, 4), 7.35 (m, 4). These complexes were used shortly after their preparation, as their chloroform solutions showed gradual decomposition; their instability precluded elemental analyses.

Acknowledgement.

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